Handbook on
Adverse DRUG REACTIONS in TB Treatment

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Pharmacology of Antitubercular Drugs Used in Newly Diagnosed Patients of Tuberculosis

ISONIAZID

It is the hydrazide of isonicotinic acid. It is primarily bactericidal.

Mechanism of Action

It is a prodrug converted into the active drug by mycobacterial catalase-peroxidase. It inhibits the synthesis of mycolic acids which are a part of the mycobacterial cell wall. Resistance to it develops by mutation in at least five of different genes (Kat G, Inh A, Ahp C, Kas A, Ndb), more likely to Inh A.

Distribution

It diffuses readily into all body fluids and cells, e.g. pleural fluid, ascitic, cerebrospinal fluid (CSF) (especially with inflamed meninges), into the caseous material, etc.

Metabolism

It is extensively metabolized in liver, most important pathway being acetylation including fast and slow acetylators.

Excretion

Majority of the dose of isoniazid is excreted in the urine within 24 hours. Excretory products result from enzymatic acetylation and enzymatic hydrolysis.

Preparation and Dose

Isoniazid is supplied in 50 mg, 100 mg and 300 mg tablets or as an elixir containing 50 mg/5 mL. Combined preparations with rifampicin, ethambutol, and pyrazinamide are available. The dose for daily therapy is 5 (4–6) mg/kg, i.e. 300 mg. In twice weekly regimen dosage is 15 (13–17) mg/kg/day and in thrice weekly regimen dosage is 10 (8–12) mg/kg/day.

Side Effects

Common side effects include fever, rash, jaundice (hepatitis), peripheral neuritis and hypersensitivity reaction. Rare side effects include hematological (anemia, thrombocytopenia, agranulocytosis, eosinophilia), vasculitis, neurological disturbances (dizziness, ataxia, toxic encephalopathy), psychiatric disturbances (euphoria, psychosis) and some miscellaneous side effects like dryness of mouth, urinary retention and epigastric distress, gynecomastia.

Renal Disease

Clearance of isoniazid is dependent only to a small degree on the status of renal function but patients who are slow acetylators of the drug may accumulate toxic concentrations if their renal function is impaired.

Pregnancy

Isoniazid is safer in pregnancy.

Contraindications

Isoniazid should not be given in known hypersensitivity and active liver disease.

Overdosage

Overdosage of isoniazid produce nausea, vomiting, dizziness, blurring of vision and slurring of speech. Massive dosage results in unconsciousness followed by respiratory depression and stupor. Severe intractable seizure may occur. Treatment consists of induced emesis, gastric lavage, activated charcoal, antiepileptic and IV sodium bicarbonate. Hemodialysis may be of value. Administration of large doses of pyridoxine is necessary to prevent seizures.

RIFAMPICIN

It is a semi-synthetic-derivative of rifamycin B. It is a bactericidal drug. It is produced by *Streptomyces mediterranei*.

Mechanism of Action

It inhibits DNA dependant RNA synthesis, i.e. it inhibits DNA dependant RNA polymerase of mycobacteria. Rifampicin should be given preferably 30 minutes before the meals since absorption is reduced when the drug is taken with food.

Distribution

Rifampicin is distributed throughout the body and is present in effective concentrations in many organs and body fluids including the CSF. The drug

imparts an orange-red color to the urine, feces, saliva, sputum, tears and sweat.

Excretion

The drug is deacetylated in the liver. About 30% of the drug is excreted in urine and about 65% in feces.

Preparation and Dose

Rifampicin is available as capsule or tablets of 150 mg, 300 mg, 450 mg, and 600 mg and as syrup containing 100 mg/5 mL. Combined preparations with isoniazid, and with isoniazid plus pyrazinamide are also available.
The dose for daily therapy being 10 (8–12) mg/kg/day (maximum 600 mg) and it is same in twice or thrice weekly regimen.

Side Effects

Common side effects include gastrointestinal upset (nausea, vomiting, abdominal pain), fever, rash, influenza-like syndrome. Moderate rises in serum concentrations of bilirubin and transaminases are common at the outset of treatment but it is transient and without clinical significance. Dose related hepatitis can also occur but it is less common. Rare side effects include neurological disturbances, hepatitis, hypersensitivity reactions, thrombocytopenia temporary oliguria, exfoliative dermatitis (especially in HIV patients), hemolytic anemia.

Renal Disease

Adjustment of dosage is not necessary in patients with impaired renal function.

Pregnancy

Rifampicin is safer in pregnancy.

Contraindications

Rifampicin is contraindicated in case of hypersensitivity and hepatic dysfunction.

Overdosage

Overdosage of rifampicin can be reverted by gastric lavage if undertaken within a few hours of ingestion. Very large dosage may depress central nervous system. There is no specific antidote and treatment is supportive.

ETHAMBUTOL

It is a synthetic congener of 1, 2-ethanediamine. It is a bacteriostatic drug.

Mechanism of Action

It interferes with mycolic acid incorporation in cell wall and has been shown to inhibit RNA synthesis. Bacterial resistance to drug develops in vivo via single amino acid change in embA genes when given in absence of another effective agent.

Distribution

It is widely distributed but penetrates meninges incompletely.

Excretion

It is excreted in urine by glomerular filtration and tubular secretion.

Preparation and Dose

Ethambutol is supplied in 400 mg, 600 mg, 800 mg and 1000 mg tablets. Combined preparations with isoniazid are available.

The dosage for daily therapy being 15 (15–20) mg/kg/day and in twice weekly regimen dosage is 45 (40–50) /mg/kg/day and in thrice weekly regimen dosage is 30 (25–35) mg/kg/day.

Pregnancy

Ethambutol is safer in pregnancy.

Side Effects

Common side effects include retrobulbar optic neuritis and hyperuricemia. Rare side effects include fever, rash, hypersensitivity reaction, gastrointestinal upset, neurological disturbances (dizziness, confusion and hallucinations), thrombocytopenia.

Renal Disease

There is significant renal excretion of ethambutol and hence dose adjustment is required in patients with renal insufficiency.

Contraindications

Ethambutol is contraindicated in patients with known hypersensitivity, previously existing visual disorder and renal failure.

Overdosage

Overdosage of ethambutol can be reverted by induced emesis and gastric lavage if undertaken within a few hours of ingestion. Subsequently, dialysis may be of value. There is no specific antidote and treatment is supportive.

PYRAZINAMIDE

It is a synthetic pyrazine analogue of nicotinamide. It is a bactericidal drug. It is more active in acidic medium. Hence, it acts on intracellular bacilli as well as on bacilli at sites of inflammatory response.

Mechanism of Action

It inhibits mycobacterial mycolic acid synthesis by acting on mycobacterial fatty acid synthase I gene.

Distribution

It is widely distributed in body and has good penetration in CSF.

Excretion

It is extensively metabolized in liver and excreted in urine.

Preparation and Dose

The drug is available in 500 mg, 1,000 mg and 1,500 mg or combined preparation with rifampicin plus isoniazid. The dose for daily patients being 25 (20–30) mg/kg and in twice weekly regimen dosage is 50 (40–60)/mg/kg/day and in thrice weekly regimen dosage is 35 (30–40) mg/kg/day.

Pregnancy

Pyrazinamide is safer in pregnancy.

Side Effects

Common side effects include hepatitis and hyperuricemia. Rare side effects include fever, rashes, loss of diabetes control and gastrointestinal upset and thrombocytopenia.

Renal Disease

There is significant renal excretion of metabolites of pyrazinamide and hence dose adjustment is required in patients with renal insufficiency.

Contraindications

Pyrazinamide is contraindicated in known hypersensitivity and hepatic dysfunction.

Overdosage

Overdosage of pyrazinamide may result in acute liver damage and hyperuricemia. It is reverted by gastric lavage and induced emesis if undertaken within a few hours of ingestion. There is no specific antidote.

STREPTOMYCIN

It is an aminoglycoside antibiotic derived from *Streptomyces griseus*. It is bactericidal drug. It acts only on extracellular bacilli.

Mechanism of Action

Streptomycin binds to several sites at 30S and 50S subunits of the ribosome as well as to their interface thereby interfering with polysome formation and causing misreading of mRNA code.

Distribution

It penetrates tubercular cavities but it does not penetrate cell walls or normal biological membranes such as the meninges or the pleura unless inflammatory changes have taken place. It crosses the placenta and fetal serum levels are about half those in maternal blood.

Excretion

It is excreted unchanged in the urine mainly by glomerular filtration.

Preparation and Dose

Streptomycin sulfate for intramuscular injection is supplied as a powder in vials and should be reconstituted immediately before use. The dose for daily therapy being 15 (range 12–18) mg/kg/day and same in twice or thrice weekly regimen. Patients aged over 60 years may not be able to tolerate more than 500–750 mg daily.

Side Effects

Common side effects are pain at site of injection, auditory ototoxicity, vestibular toxicity and nephrotoxicity. Rare side effects include hemolytic anemia, agranulocytosis, thrombocytopenia and hypersensitivity reaction.

Renal Disease

Because of an increased risk of nephrotoxicity and ototoxicity, streptomycin should be avoided in patients with renal failure.

Pregnancy

It should not be given in pregnancy as it crosses the placental barrier producing ototoxicity (auditory nerve impairment) and renal impairment in the fetus.

Contraindications

It should not be given in known hypersensitivity, auditory nerve impairment, myasthenia gravis and renal failure.

Overdosage

In case of overdosage of streptomycin, hemodialysis may be beneficial. There is no specific antidote and treatment is supportive.

FURTHER READINGS

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Handbook on
Adverse DRUG REACTIONS in TB Treatment

Salient Features

- Comprehensive well-referenced handbook, which contains a plethora of knowledge
- Defines a practical approach to every aspect of adverse drug reactions in tuberculosis treatment
- Covers all the aspects ranging from epidemiology of adverse drug reactions in new and drug-resistant patients
- Includes the case-based approach to treatment of tuberculosis, multi-drug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) in special situations such as pregnancy, renal insufficiency and liver diseases
- Chapters are organized in a systematic way for easy understanding and for practical approach with illustrative cases
- Serves as a practical guide for undergraduate and postgraduate medical students, practitioners, program managers and healthcare workers in TB control.

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